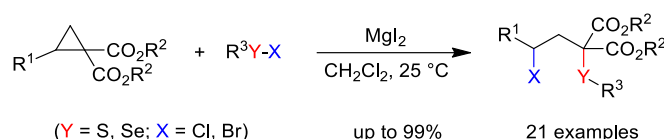


# Ring-Opening 1,3-Halochalcogenation of Cyclopropane Dicarboxylates

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Supporting Information Placeholder



**ABSTRACT:** Donor-acceptor cyclopropanes with two geminal carboxylic esters are reacted with chalcogenyl chlorides and bromides to afford ring-opened products bearing the halogen atoms in the 1-position, adjacent to the donor, and the chalcogenyl residue in 3-position next to the two acceptor groups. A variety of different donors (*e.g.* aryl, N, and O) are used. The stereospecificity of the reaction is demonstrated by using a chiral starting material.

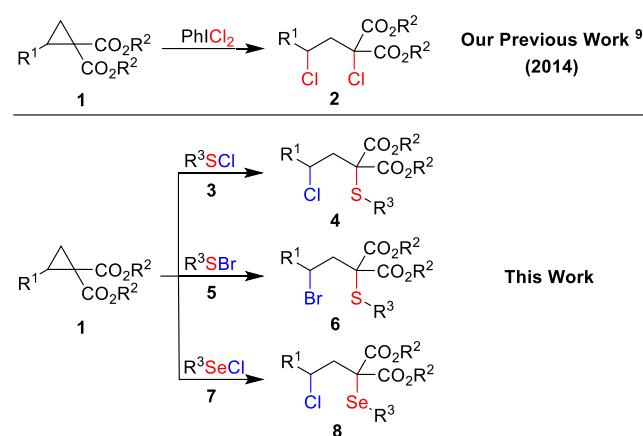
During the last decade, donor-acceptor (D-A) cyclopropanes have enjoyed a renaissance as easily available building blocks.<sup>1</sup> Although the basic chemistry in this field was developed by Wenkert and Reissig<sup>2</sup> in the 1970s and 1980s, many groups have recently utilized the unique features of this special class of three-membered rings. These highly polarized strained systems easily undergo cycloadditions,<sup>3</sup> rearrangements<sup>4,5</sup> and ring-opening reactions. Thus, they are an ideal starting point for the synthesis of carbo- and heterocycles and have been used in the preparation of natural products.<sup>6</sup>

Cycloaddition and rearrangement reactions of D-A cyclopropanes commonly allow a rapid increase of complexity whereas ring-opening reactions decrease the complexity by transforming the cyclopropane into an aliphatic chain. A variety of heteronucleophiles such as phenols, amines, azides or indoles have been employed to open the ring.<sup>7</sup> As a result, the nucleophile is located next to the donor while the negative charge next to the acceptor is captured by a proton. In order to further weaken the bond between donor and acceptor and to promote the attack, Lewis acids are commonly applied. Whereas the transfer of a nucleophile to position 1 and a proton to position 3 has often been reported, only a few examples of ring-opening reactions exist in which two non-hydrogen substituents were attached to the 1- and 3-positions next to the donor and acceptor.<sup>8</sup> Recently, we found that cyclopropane dicarboxylates **1** react with Willgerodt's reagent (PhICl<sub>2</sub>) to yield 1,3-dichlorinated compounds **2** (Scheme 1).<sup>9</sup> Sparr and Gilmour even performed enantioselective 1,3-dichlorinations of *meso*-cyclopropyl aldehydes using an organocatalytic approach.<sup>10</sup>

After our initial attempts with the ring-opening 1,3-dichlorination, we considered whether we might trigger other ring-opening 1,3-additions of cyclopropane dicarboxylates by using strongly polarized bonds of the type RY-X. Prototypes of such species are provided by the sulfonyl and selenyl halides **3**, **5**, and **7**. The higher electronegativity of the halogen in comparison to the chalcogen efficiently polarizes the bond. Thus, we envisioned that the electrophilic part of the cyclopropane, the

center next to the donor, might add the halide and the nucleophilic part, next to the two acceptor moieties, would be captured by the positively polarized chalcogen. This assumption was corroborated by early work from Reissig and Reichelt that led to 2-chalcogenyl-substituted 4-oxoesters when TMSO-substituted cyclopropanes were treated with chalcogenyl chlorides.<sup>11</sup>

## Scheme 1. Ring-Opening 1,3-Dichlorination of Cyclopropane Dicarboxylates and our Extension to 1,3-Halochalcogenation.

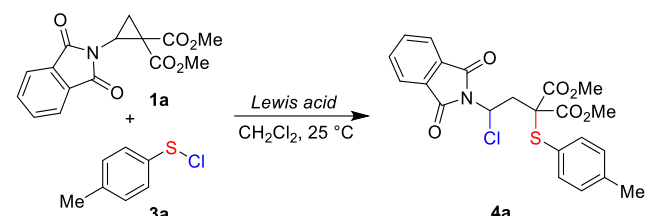


At the outset of our studies, D-A cyclopropane **1a** was chosen to explore suitable conditions for the expected process. As component to be added we chose *p*-tolylsulfonyl chloride **3a**, which is easily available from the respective thiophenol and *N*-chlorosuccinimide;<sup>12</sup> as donor we employed phthalimide.

Initial experiments using FeCl<sub>2</sub>, which is known to act as radical initiator in combination with sulfonyl chlorides,<sup>13</sup> showed no formation of the desired product (Table 1). Incorporation of stronger Lewis acids such as Sc(OTf)<sub>3</sub> (entry 2), Yb(OTf)<sub>3</sub>,

$\text{BF}_3 \cdot \text{OEt}_2$  or  $\text{TiCl}_4$  led to decomposition of the starting materials. More promising results could be achieved with  $\text{FeCl}_3$ , indicating that the desired product is formed, and  $\text{ZnBr}_2$ , giving rise to 50% of **4a** in addition to some unspecified byproducts. Finally the utilization of 10 mol %  $\text{MgI}_2$  as Lewis acid, combined with an increase of the amount of sulfonyl chlorides to 1.5 equivalents and a shortening of the reaction time to 5 minutes, yielded **4a** in 91% yield.

**Table 1. Optimization of the 1,3-Chlorosulfonylation.**



entry	Lewis acid	<b>3a</b> (equiv)	<i>t</i> (h)	yield (%)
1	$\text{FeCl}_2$	1.1	24	-
2	$\text{Sc}(\text{OTf})_3$	1.1	24	decomp.
3	$\text{FeCl}_3$	1.1	24	complex mixture <sup>[a]</sup>
4	$\text{ZnBr}_2$	1.1	3	50 + by-products
5	$\text{MgI}_2$	1.1	0.5	81
6	$\text{MgI}_2$	1.5	0.08	91

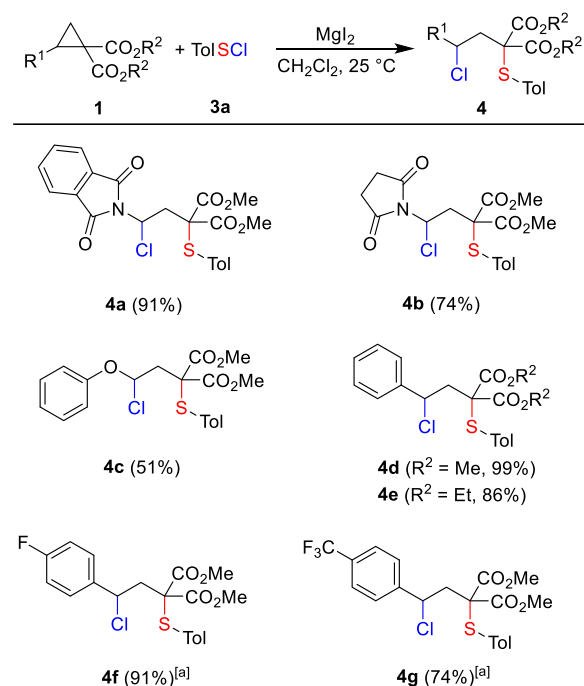
Reaction conditions: **1a** (0.1 mmol),  $\text{CH}_2\text{Cl}_2$  (0.1 M, with respect to the cyclopropane), 10 mol % of Lewis acid used, reactions performed at ambient temperature. <sup>[a]</sup> Desired product was found in the mixture.

With optimized conditions in hand, the scope of this 1,3-chlorosulfonation reaction was examined. We started with a variation of the donor ( $\text{R}^1$ ) at the three-membered ring (Scheme 2). Optimization had originally been performed with the nitrogen donor phthalimide; thus, succinimide was also tested and provided a yield of **4b** in 74%. Oxygens are other markedly electron-releasing donors, and a phenoxy-substituted cyclopropane afforded the desired product **4c** in 51%. Also several arene units differing in their electron-donating ability were subjected to the reaction conditions. The transformations proceeded smoothly and furnished the desired products **4d–4g** in yields of 74–99%. Cyclopropanes with very electron-rich arene units such as *p*-MeOPh underwent electrophilic aromatic substitution with a sulfenium ion resulting in a mixture of products.

Next, the scope of various sulfonyl chlorides was tested (Scheme 3). Electron-poor aryl residues (**4h**, **4o**), but also electron-rich (**4i**) and fluoro-substituted (**4j**) residues, were compatible with the reaction. The use of bulky *o*-tolyl sulfonyl chloride provided **4k** in good yield of 83%. Aliphatic sulfonyl chlorides also participated in the reaction and a similar yield was obtained (77%). Even a thiocarbonate was successfully introduced by the reaction of the cyclopropane with  $\text{ClS}(\text{CO})\text{OMe}$ , affording the respective product **4m** in 90% yield. The pseudohalogen  $\text{ClSCN}$  is easily available from the reaction of lead(II) thiocyanate and sulfur chloride, and we therefore employed this reagent too to affect a ring-opening under our conditions; the transformation yielded the respective thiocyanate **4n** in 96% yield. Since the sulfur is still positively polarized, thiocyanates have

been utilized as useful precursors for further reactions with carbon nucleophiles with loss of cyanide (e.g. leading to thioalkynes).<sup>14</sup>

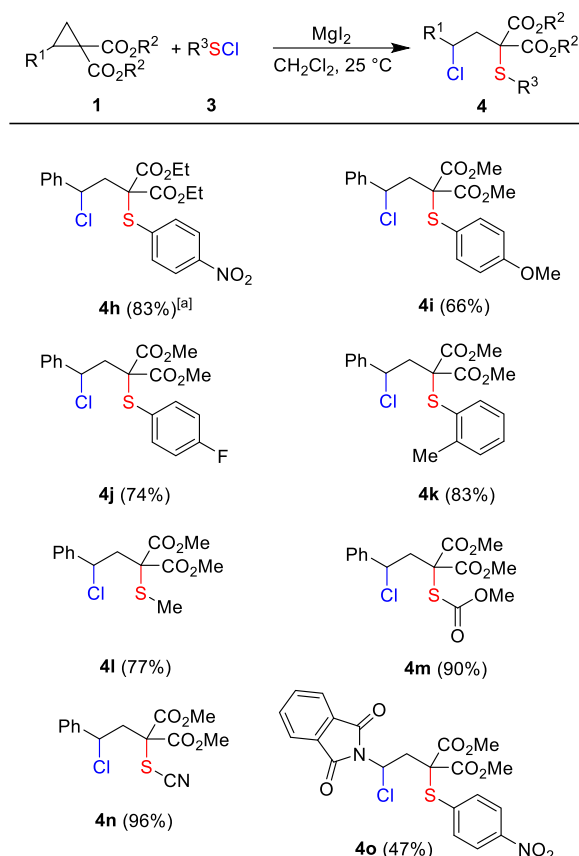
**Scheme 2. 1,3-Chlorosulfonylation of Donor-Acceptor Cyclopropanes with *p*-Tolylsulfonyl Chloride.**



Reaction conditions: **1** (0.2 mmol) and **3a** (1.5 – 2.0 equiv),  $\text{MgI}_2$  (10 mol %),  $\text{CH}_2\text{Cl}_2$  (0.1 M), reaction time: 5 min – 3 h. All yields represent isolated 1,3-functionalized products. <sup>[a]</sup> 0.1 mmol of **1** was used.

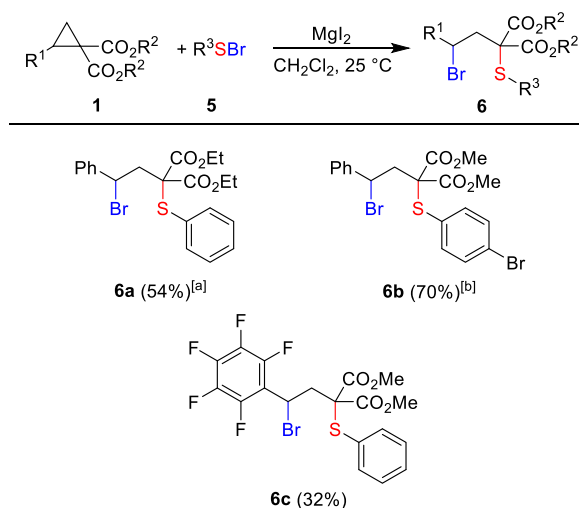
Next, we addressed the question whether sulfonyl bromides also react in an analogous way. These were obtained from the thiol and a solution of *N*-bromosuccinimide (NBS). To precipitate the resulting succinimide, the mixture was suspended with *n*-pentane and then filtered. Removal of the solvent *in vacuo* gave the sulfonyl bromide, which was used without further purification. Since sulfonyl bromides are more sensitive than sulfonyl chlorides, we employed only aryl sulfonyl bromides **5** and used more equivalents than in the experiments described before. Scheme 4 depicts three examples of 1,3-bromosulfonation. Much longer reactions times (20–24 h) were required for complete conversion, which might be attributed to the much less pronounced polarization of the S–Br bond. The yields of **6** ranging from 32–70% were much lower than for the lighter counterparts; nevertheless, even when the strongly electron-withdrawing pentafluorophenyl residue was used as a donor, it afforded product **6c** in 32% yield.

**Scheme 3. 1,3-Chlorosulfonylation of Phenyl- and Imido-Substituted Cyclopropanes with Several Sulfonyl Chlorides,  $\text{ClS}(\text{CO})\text{OMe}$ , and  $\text{ClSCN}$ .**



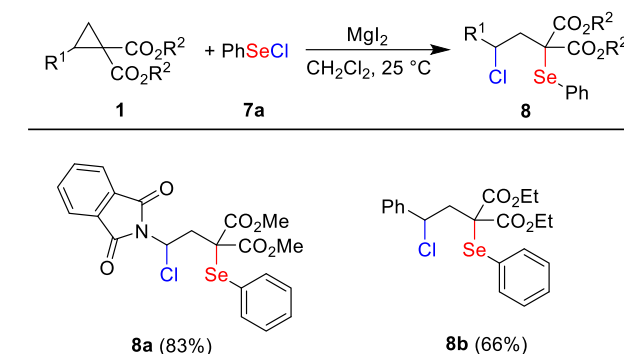
Reaction conditions: **1** (0.1 mmol) and **3** (1.5 – 5.0 equiv),  $\text{MgI}_2$  (10 mol %),  $\text{CH}_2\text{Cl}_2$  (0.1 M), reaction time: 15 min – 20 h. All yields represent isolated 1,3-functionalized products. <sup>[a]</sup> 0.2 mmol of **1** was used.

#### Scheme 4. 1,3-Bromosulfenation of Donor-Acceptor Cyclopropanes with Sulfenyl Bromide.



phenylselenenyl chloride (Scheme 5). The corresponding selenium-containing products were obtained in 66% and 83% yield. Notably, formation of **8a** was much faster than **8b**. Because of the relative instability of corresponding aliphatic selenenyl chlorides, we did not attempt transformations with these reagents. Analogous experiments with phenylselenenyl bromide and respective thio- and selenocyanates showed no conversion, and the starting material was recovered.

#### Scheme 5. 1,3-Chloroselenation of Donor-Acceptor Cyclopropanes with Phenylselenenyl Chloride.

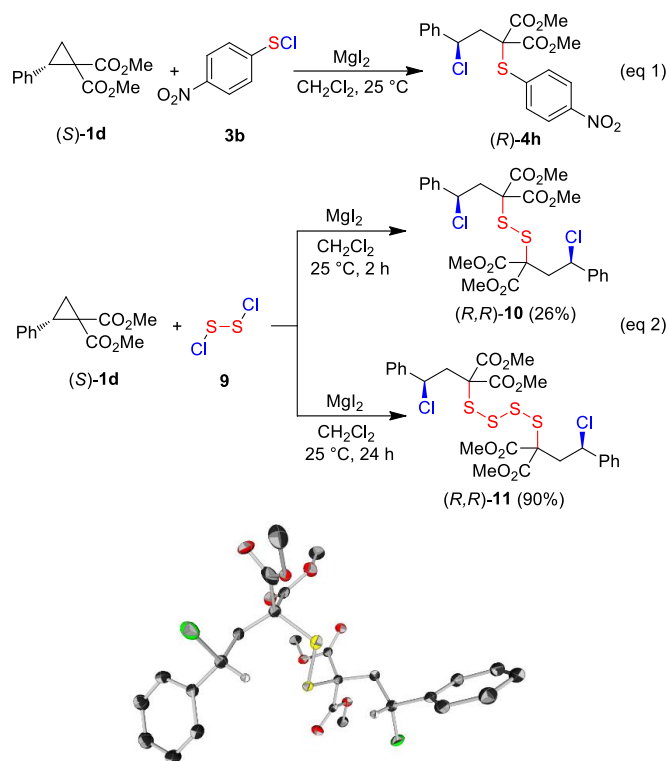


Finally, we explored the stereospecificity of the ring-opening 1,3-chlorosulfenation using enantioenriched (95% *ee*) phenyl-substituted cyclopropane (*S*)-**1d**. *p*-Nitrophenylsulfenyl chloride (**3b**) reacted with almost complete stereospecificity giving (*R*)-**4h** in quantitative yield and 88% *ee* as revealed by chiral HPLC (Scheme 6 eq 1 and Supporting Information). Mechanistically, this process might be explained *via*  $\text{S}_{\text{N}}2$ -like attack of the chloride (from  $\text{RSCl}$ ) to the cyclopropane, which then further reacts with the sulfenium ion to give (*R*)-**4h**. In addition, we found that  $\text{S}_2\text{Cl}_2$  was also able to undergo the reaction (Scheme 6 eq 2). Since both termini of the  $\text{S}_2$  moiety react, we used again (*S*)-**1d** in order to exclude the possibility of generating a diastereomeric mixture. The desired product **10** was obtained in poor yield of 26% after 2 h; longer reaction times furnished a product with an  $\text{S}_4$  chain (**11**) in much higher yield (90%). For **10**, a X-ray crystallographic analysis confirmed the expected structure and demonstrated the inversion of the stereocenter during the transformation. The molecular structure of this compound is depicted in Figure 1.

#### Scheme 6. (eq 1) Stereospecificity of the 1,3-Chlorosulfenation. (eq 2) Transformation with $\text{S}_2\text{Cl}_2$ to Dimeric Structures.

Reaction conditions: **1** (0.1 mmol) and **5** (3.0 equiv),  $\text{MgI}_2$  (10 mol %),  $\text{CH}_2\text{Cl}_2$  (0.1 M), reaction time: 20–24 h. All yields represent isolated 1,3-functionalized products. <sup>[a]</sup> 0.2 mmol of **1** used. <sup>[b]</sup> 10 equiv of **5** used.

Moreover, our reaction conditions were successfully extended to the synthesis of 1,3-chloroselenated products. Both the phthalimide- and the phenyl-substituted three-membered ring were converted smoothly with commercially available



**Figure 1.** Molecular structure (50% ellipsoid probability) of **10** in the solid state. Oxygen atoms are shown in red, sulfur atoms in yellow and chlorine atoms in green. Hydrogen atoms are omitted.<sup>15,16</sup>

In conclusion, we have developed novel 1,3-haloalchalcogenation reactions of cyclopropane dicarboxylates. A variety of donor-acceptor cyclopropanes were converted either with readily available sulfonyl chlorides, sulfonyl bromides or selenyl chlorides. Oxygen and nitrogen and even aromatic systems can be successfully employed as donors. Magnesium iodide proved to be the Lewis acid of choice. Further work with other highly polarized reagents to trigger other ring-opening 1,3-addition processes is in progress in our laboratory.

## ASSOCIATED CONTENT

### Supporting Information

Detailed experimental procedures, analytical data for all new compounds, and crystal data (CIF) for **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

- (1) For reviews on D-A cyclopropanes: (a) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151-1196. (b) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321-347. (c) Agrawal D.; Yadav, V. K. *Chem. Commun.* **2008**, 6471-6488. (d) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051-3060. (e) De Simone, F.; Waser, J. *Synthesis* **2009**, 3353-3374. (f) Lebold, T. P.; Kerr, M. A. *Pure Appl. Chem.* **2010**, *82*, 1797-1812. (g) Mel'nikov, M. Y.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V. *Mendeleev Commun.* **2011**, *21*, 293-301. (h) Wang, Z. W. *Synlett* **2012**, 2311-2327. (i) Tang, P.; Qin, Y. *Synthesis* **2012**, 2969-2984. (j) Cavitt, M. A.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804-818. (k) Schneider, T. F.; Kaschel, J.; Werz, D. B. *Angew. Chem. Int. Ed.* **2014**, *53*, 5504-5523. (l) Novikov, R. A.; Tomilov, Y. V. *Mendeleev Commun.* **2015**, *25*, 1-10. (m) Grover, H. K.; Emmett, M.; R.; Kerr, M. A. *Org. Biomol. Chem.* **2015**, *13*, 655-671. (n) O'Connor, N. R.; Wood, J. L.; Stoltz, B. M. *Isr. J. Chem.* **2016**, *56*, 431-444.
- (2) (a) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Chou, K. J. *J. Am. Chem. Soc.* **1977**, *99*, 4778-4782. (b) Reissig, H.-U.; Hirsch, E. *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 813-814. (c) Brückner, C.; Reissig, H.-U. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 588-589.
- (3) (a) Zhang, J.; Xing, S.; Ren, J.; Jiang, S.; Wang, Z. *Org. Lett.* **2015**, *17*, 218-221. (b) Xu, H.; Hu, J.-L.; Wang, L.; Liao, S.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 8006-8009. (c) Cheng, Q.-Q.; Qian, Y.; Zavalij, P. Y.; Doyle, M. P. *Org. Lett.* **2015**, *17*, 3568-3571. (d) Garve, L. K. B.; Pawliczek, M.; Wallbaum, J.; Jones, P. G.; Werz, D. B. *Chem. Eur. J.* **2016**, *22*, 521-525. (e) Garve, L. K. B.; Petzold, M.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2016**, *18*, 564-567. (f) Kaicharla, T.; Roy, T.; Thangaraj, M.; Gonnade, R. G.; Biju, A. T. *Angew. Chem. Int. Ed.* **2016**, *55*, 10061-10064. (g) Sabbatani, J.; Maulide, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 6780-6783.
- (4) Computational investigation of D-A cyclopropane rearrangements: Schneider, T. F.; Werz, D. B. *Org. Lett.* **2011**, *13*, 1848-1851.
- (5) (a) Brand, C.; Rauch, G.; Zanon, M.; Dittrich, B.; Werz, D. B. *J. Org. Chem.* **2009**, *74*, 8779-8786. (b) Schneider, T. F.; Kaschel, J.; Dittrich, B.; Werz, D. B. *Org. Lett.* **2009**, *11*, 2317-2320. (c) Schneider, T. F.; Kaschel, J.; Awan, S. I.; Dittrich, B.; Werz, D. B. *Chem. Eur. J.* **2010**, *16*, 11276-11288. (d) Kaschel, J.; Schneider, T. F.; Kratzert, D.; Stalke, D.; Werz, D. B. *Angew. Chem. Int. Ed.* **2012**, *51*, 11153-11156. (b) Kaschel, J.; Schneider, T. F.; Kratzert, D.; Stalke, D.; Werz, D. B. *Org. Biomol. Chem.* **2013**, *11*, 3494-3509. (e) Kaschel, J.; Schmidt, C. D.; Mumby, M.; Kratzert, D.; Stalke, D.; Werz, D. B. *Chem. Commun.* **2013**, *49*, 4403-4405. (f) Schmidt, C. D.; Kaschel, J.; Schneider, T. F.; Kratzert, D.; Stalke, D.; Werz, D. B. *Org. Lett.* **2013**, *15*, 6098-6101.
- (6) (a) Kreuzer, A.; Kerres, S.; Ertl, T.; Rücker, H.; Amslinger, S.; Reiser, O. *Org. Lett.* **2013**, *15*, 3420-3423. (b) Racine, S.; de Nanteuil, F.; Serrano, E.; Waser, J. *Angew. Chem. Int. Ed.* **2014**, *53*, 8484-8487. (c) Gharpure, S. J.; Nanda, L. N.; Shukla, M. K. *Org. Lett.* **2014**, *16*, 6424-6427.
- (7) (a) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6838-6840. (b) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809-2812. (c) Sridhar, P. R.; Venkumar, P. *Org. Lett.* **2012**, *14*, 5558-5561. (d) Emmett, M. R.; Grover, H. K.; Kerr, M. A. *J. Org. Chem.* **2012**, *77*, 6634-6637. (e) So, S. S.; Auvi, T. J.; Garza, V. J.; Mattson, A. E. *Org. Lett.* **2012**, *14*, 444-447. (f) Zhou, Y.-Y.; Wang, L.-J.; Li, J.; Sun, X.-L.; Tang, Y. *J. Am. Chem. Soc.* **2012**, *134*, 9066-9069. (g) Braun, C. M.; Shema, A. M.; Dulin, C. C.; Nolin, K. A. *Tetrahedron Lett.* **2013**, *54*, 5889-5891. (h) Nickerson, D. M.; Angeles, V. V.; Auvi, T. J.; So, S. S.; Mattson, A. E. *Chem. Commun.* **2013**, *49*, 4289-4291. (i) Wales, S. M.; Walker, M. M.; Johnson, J. S. *Org. Lett.* **2013**, *15*, 2558-2561. (j) de Nanteuil, F.; Loup, J.; Waser, J. *Org. Lett.* **2013**, *15*, 3738-3741. (k) Martin, M. C.; Patil, D. V.; France, S. J. *Org. Chem.* **2014**, *79*, 3030-3039. (l) Ivanov, K. L.; Villemson, E. V.; Budynina, E. M.; Ivanova, O. A.; Trushkov, I. V.; Melnikov, M. Y. *Chem. - Eur. J.* **2015**, *21*, 4975-4987. (m) Kang, Q.-K.; Wang, L.; Liu, Q.-J.; Li, J.-F.; Tang, Y. *J. Am. Chem. Soc.* **2015**, *137*, 14594-14597. (n) Xia, Y.; Liu, X.; Zheng, H.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 227-230. (o) Xia, Y.; Lin, L.; Chang, F.; Fu, X.; Liu, X.; Feng, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 13748-13752. (p) Tejeda, J. E. C.; Landschoot, B. K.; Kerr, M. A. *Org. Lett.* **2016**, *18*, 2142-2145.

- (8) (a) Skell, P. S.; Day, J. C.; Shea, H. K. *J. Am. Chem. Soc.* **1972**, *94*, 1126-1129. (b) Lambert, J. B.; Schulz, W. J., Jr.; Mueller, P. H.; Kobayashi, K. *J. Am. Chem. Soc.* **1984**, *106*, 792-793.
- (9) Garve, L. K. B.; Barkawitz, P.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2014**, *16*, 5804-5807
- (10) Sparr, C.; Gilmour, R. *Angew. Chem. Int. Ed.* **2011**, *50*, 8391-8395.
- (11) Reissig, H.-U.; Reichelt, I. *Tetrahedron Lett.* **1984**, *25*, 5879-5880.
- (12) Huang, H.; Fan, J.; He, G.; Yang, Z.; Jin, X.; Zhu, H. *Chem. Eur. J.* **2016**, *22*, 2532-2538.
- (13) Iwasaki, M.; Fujii, T.; Nakajima, K.; Nishihara, Y. *Angew. Chem. Int. Ed.* **2014**, *50*, 13880-13884.
- (14) (a) Werz, D. B.; Gleiter, R. *J. Org. Chem.* **2003**, *68*, 9400-9405. (b) Werz, D. B.; Gleiter, R.; Rominger, F. *J. Org. Chem.* **2004**, *69*, 2945-2952
- (15) (a) Kottke, T.; Stalke, D. *J. Appl. Crystallogr.* **1993**, *26*, 615-619. (b) Agilent Technologies, CrysAlisPro. Version 1.171.36.28 Oxford, UK, **2013**. (c) Sheldrick, G. M.; SHELXL-97, University of Göttingen, Germany **1997**. (d) Sheldrick, G. M. *Acta Crystallogr. Sect. A* **2008**, *64*, 112-122.
- (16) The CIF file has been deposited with the Cambridge Crystallographic Data Centre as "supplementary publication no. CCDC-1507090 (**10**)". Copies can be obtained via email: data\_request@ccdc.cam.ac.uk.